Clinical Management of NASH: Diet and Nutrition

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The Greater the Obesity the Greater Is the NAFLD-Related Liver Damage

Case-control study of veterans, n= 399 with biopsy

BMI independently predicts severity

- NAFLD/NASH Cirrhosis: 1.4 (1.2-1.6)
- NAFLD/NASH with Stage 1-3 Fibrosis: 1.4 (1.2-1.6)
- NASH without Fibrosis: 1.2 (1.1-1.4)
- NAFL Steatosis: 1.3 (1.2-1.5)
- Control: 1 (reference)

Adjusted for: age, ethnicity, DM, hypertension, dyslipidemia, platelets, AST/ALT ratio and smoking.

Visceral Adipose Tissue Associated with Liver Damages

- 798 morbid obese patients undergoing bariatric surgery
- Liver biopsies
- DXA

Effect of Weight Loss on NAFLD: A Systematic Review and Meta-Analysis

- 22 RCTs with 2588 participants with NAFLD

Steatosis
ALT
NAS

Fibrosis
Liver stiffness

Placebo Response in RCTs of Pharmacotherapies for NASH

25% of patients given placebo improved NAS by ≥ 2 points

21% of patients given placebo improved fibrosis by ≥ 1 point

Han MAT. Clin Gastroenterol Hepatol. 2019.
Effect of Diet with or Without Physical Activity on Liver and Visceral Fat

- 18-month RCT, 278 obese adults

<table>
<thead>
<tr>
<th>18-Month Changes</th>
<th>Low-Fat Diet</th>
<th>Mediterranean/Low-Carbohydrate Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PA− (Ref)</td>
<td>PA+</td>
</tr>
<tr>
<td>Visceral adipose tissue, cm²</td>
<td>−32.9±33.5</td>
<td>−48.9±43.0†</td>
</tr>
<tr>
<td>Intrahepatic fat, %, absolute units</td>
<td>−3.72±7.12</td>
<td>−3.88±6.32</td>
</tr>
</tbody>
</table>

Beneficial Effects of Lifestyle Intervention in Non-Obese Patients with NAFLD

- RCT
- 154 NAFLD patients
- 12-month lifestyle intervention

- Remission of NAFLD in a dose-dependent manner in both lean and obese
- Reduction of weight gain even within the normal BMI range
- Reduced intake of fructose/ sugared soft drinks
- Reduced intake of dietary cholesterol (?)
- Physical activity- decrease visceral fat

WC: plus 5.9±0.4  WC: plus 11.6±0.8

Ultra Processed Food and Drinks: Major Source of Added Sugar, High Energy Dense Foods & Low Nutritional Value

Ultra-Processed Foods Are Not ‘Real Food’

- Formulations of food substances modified by chemical processes
- ‘Cosmetic additives’ Flavours, colours, emulsifiers
- Hyper-palatable food and drink products

Practical way to identify if a product is ultra-processed

- List of ingredients contains substances rarely used in kitchens
  - Hydrolysed proteins
  - Fructose, high-fructose corn syrup
  - Hydrogenated oil
  - Cosmetic additives

Consumption of Ultra-Processed Foods Increases Morbidity and Mortality

- 104,980 adult participants from the French NutriNet-Santé cohort

10% increase in the proportion of ultraprocessed food Consumption

14% higher risk of all-cause mortality

Cancer incidence by quarters of ultra-processed food

Ultra-Processed Diets Cause Excess Calorie Intake and Weight Gain – Randomized Cross-Over Trial of Ad Libitum Food Intake

- 20 adults
- NIH Clinical Center
- Weight changes highly correlated with energy intake ($r = 0.8$, $p < 0.0001$)
- Limiting consumption of ultra-processed foods may be an effective strategy for obesity prevention and treatment

Hall KD. *Cell Metabolism*. 2019.
Food Sources and Implications of Advanced-Glycation End-Products (AGEs)

- High fat/sugar food
- High heat-processed food and beverages
  - Processed and well done red meat

- Metabolic alterations
  - Oxidative stress
  - Insulin resistance
  - Type-2 diabetes
  - Cardiovascular disease

- Liver damage
  - Fatty liver & liver inflammation
  - Liver cancer

High Red and Processed Meat Consumption Is Associated with NAFLD and Insulin Resistance

- A cross-sectional study of volunteers who participated in screening $n = 789$, 39% NAFLD (US)
Diet Associations with NAFLD in an Ethnically Diverse Population the Multiethnic Cohort

- Nested case-control
- 2,974 NAFLD cases
  - 518 with cirrhosis
  - 2,456 without cirrhosis
- 29,474 matched controls
- Cases identified using Medicare claims ICD9/10
- Controls individually matched to cases on birth year, sex, ethnicity
- FFQ

<table>
<thead>
<tr>
<th>(g/1,000 kcal/day)</th>
<th>NAFLD No Cirrhosis</th>
<th>NAFLD With Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q 1st vs. 4th OR</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
</tbody>
</table>

- **Cholesterol**
  - ≤ 75.4: 1.00 (ref.)
  - > 121.4: 1.09 (0.96-1.23) **1.52 (1.15-2.01)**
- **P-value for trend**: 0.0889 **0.0018**

- **Fiber**
  - ≤ 8.5: 1.00 (ref.)
  - > 14.0: 0.86 (0.75-0.98) **0.75 (0.55-1.02)**
- **P-value for trend**: 0.0123 **0.1018**

<table>
<thead>
<tr>
<th>(g/1,000 kcal/day)</th>
<th>NAFLD No Cirrhosis</th>
<th>NAFLD With Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total red meat</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>≤ 13.7</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>&gt; 34.0</td>
<td>1.10 (0.97-1.25)</td>
<td>1.43 (1.08-1.90)</td>
</tr>
</tbody>
</table>
- **P-value for trend**: 0.1190 **0.0121**

- **Red unprocessed meat**
  - ≤ 9.3: 1.00 (ref.)
  - > 24.1: 1.10 (0.97-1.25) **1.52 (1.15-2.01)**
- **P-value for trend**: 0.1223 **0.0033**

- **Processed red meat**
  - ≤ 3.0: 1.00 (ref.)
  - > 10.0: 1.17 (1.03-1.32) **1.31 (0.99-1.71)**
- **P-value for trend**: 0.0097 **0.1123**

- **Total poultry**
  - ≤ 11.4: 1.00 (ref.)
  - > 27.6: 1.19 (1.05-1.35) **1.03 (0.79-1.35)**
- **P-value for trend**: 0.0028 **0.7717**

Overeating Saturated Fat Promotes Fatty Liver Compared to Polyunsaturated Fat RCT

~3 muffins containing either sunflower oil (high in PUFA) or palm oil (high in SFA)
~40 grams of oil/day
Except for fat type, muffins were identical in composition

N= 60 double-blind, parallel-group, RCT

8 weeks

Saturated Fat Increases Liver Fat RCT

38 overweight subjects

A Prospective Study of Dairy Product Intake and the Risk of Hepatocellular Carcinoma in U.S. Men and Women

- 2 large prospective U.S. cohort studies, 51,418 men and 93,427 women
- Diets at baseline and updated every 2-4 years using validated FFQ

<table>
<thead>
<tr>
<th>Dairy products</th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
<th>P trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-fat dairy products</td>
<td>1 (Reference)</td>
<td>1.5 (0.95-2)</td>
<td>1.81 (1.2-3)</td>
<td>0.008</td>
</tr>
<tr>
<td>Low-fat dairy products</td>
<td>1 (Reference)</td>
<td>1.2 (0.8-1.8)</td>
<td>1.18 (0.8-1.8)</td>
<td>0.53</td>
</tr>
<tr>
<td>Butter</td>
<td>1 (Reference)</td>
<td>1.3 (0.8-2)</td>
<td>1.58 (1.1-2)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Adjusted for age, gender, race, physical activity, BMI, smoking, alcohol, coffee intake, calorie intake, aspirin use and type 2 diabetes

Effect of a Low-Free Sugar Diet in NAFLD

- An open-label, 8-week RCT
- Boys aged 11-16 years (n=40) with NAFLD
- Diet group or usual diet group
  - Provision of study meals for the entire household to restrict free sugar intake to less than 3% of daily calories

Liver fat

-1.3 kg
Independent of weight change

ALT

+0.6 kg

Individual-level measurements

Fructose Consumption Independently Associated with NASH in Children & Adolescents

- 271 obese children with NAFLD
- Liver biopsy obtained

### Adjusted association between fructose consumption & uric acid levels and NASH (NAS ≥ 5)

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fructose, g/day</td>
<td>1.612 (1.25, 1.86)</td>
<td>0.001</td>
</tr>
<tr>
<td>Uric acid, mg/dl</td>
<td>2.488 (1.87, 2.83)</td>
<td>0.004</td>
</tr>
<tr>
<td>WC, cm</td>
<td>1.842 (1.11, 1.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>3.21 (1.9, 5.72)</td>
<td>0.024</td>
</tr>
<tr>
<td>Triglyceride, mg/dl</td>
<td>1.208 (1.1, 1.58)</td>
<td>0.048</td>
</tr>
</tbody>
</table>

"Excess consumption of added sugars, especially from sugary drinks, poses health threat to children and adolescents, disproportionately affecting children of minority and low-income communities. Public policies are needed ……"

Policy statement 2019

**No Association of Fruits Intake with NAFLD**

- Cross-sectional study in Japan
- Short dietary intake questionnaire
- NAFLD diagnosed by US

**Odds ratios of non-alcoholic fatty liver disease according to quartiles of fruit intake and vegetable intake**

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women (N=1,467)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruit (g/1,000 kcal) median (range)</td>
<td>16.3 (0.0-30.5)</td>
<td>45.4 (30.8-59.9)</td>
<td>74.4 (60.0-93.1)</td>
<td>121.0 (93.2-329.5)</td>
<td></td>
</tr>
<tr>
<td>BMI adjusted OR</td>
<td>1</td>
<td>0.85 (0.49, 1.47)</td>
<td>0.90 (0.49, 1.63)</td>
<td>0.82 (0.44, 1.55)</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Men (N=977)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruit (g/1,000 kcal) median (range)</td>
<td>10.4 (0.0-18.1)</td>
<td>28.2 (18.2-39.3)</td>
<td>52.6 (39.4-67.9)</td>
<td>93.9 (68.3-301.6)</td>
<td></td>
</tr>
<tr>
<td>BMI adjusted OR</td>
<td>1</td>
<td>0.90 (0.58, 1.38)</td>
<td>0.88 (0.56, 1.37)</td>
<td>0.68 (0.42, 1.11)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

A Human & Planetary Healthy Plate

Estimated deaths prevented among adults by a global adoption of this diet

~20% of global deaths = ~ 11 million adult deaths /year

©UEG. 2018.
Improved Diet Quality Scores Associates with Reduction in Liver Fat

- Framingham Heart Study, n= 1521
- 6 years follow-up
- Semi-quantitative 126-item Harvard food frequency questionnaire – MD diet score
- Liver fat by CT

Multivariate Association of Vitamin E and C Intake and NAFLD Severity

- Cross-sectional study
- NAFLD by AUS
- Steatosis, NASH and fibrosis by FibroMax
- 714 had reliable FibroMax

<table>
<thead>
<tr>
<th>Vitamin E per 1000 Kcal (upper tertile)</th>
<th>NAFLD (n cases=305)</th>
<th>NASH ≥2 (n cases=225)</th>
<th>Fibrosis ≥F1-F2 (n cases=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5.45</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>≥ 5.45</td>
<td>0.70 (0.49-1.02)</td>
<td>0.60 (0.41-0.89)</td>
<td>0.96 (0.60-1.52)</td>
</tr>
</tbody>
</table>

OR (95% CI) P

<table>
<thead>
<tr>
<th>Vitamin C per 1000 Kcal (upper tertile)</th>
<th>NAFLD (n cases=305)</th>
<th>NASH ≥2 (n cases=225)</th>
<th>Fibrosis ≥F1-F2 (n cases=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 91.40</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>≥91.40</td>
<td>0.68 (0.47-0.99)</td>
<td>0.57 (0.38-0.84)</td>
<td>0.94 (0.58-1.51)</td>
</tr>
</tbody>
</table>

OR (95% CI) P

Adjusted for: age, gender, energy intake, BMI, physical activity, SFA intake, smoking, alcohol, fibers, cholesterol, red and/or processed meat intake.
Age-Standardised Intake of Dietary Factors Among Adults Aged 25 Years or Older at the Global and Regional Level in 2017

Daily intake of all unhealthy foods exceeds the optimal level

©UEG. 2018.
Food insecurity is associated with NAFLD among low-income adults in the US. The study used cross-sectional data from NHANES 2005–2014, involving 2627 adults in low-income households. NAFLD was assessed by the US Advanced fibrosis by NAFLD fibrosis score. OR & prevalence are adjusted for age, sex, household income, ethnicity, education, alcohol and smoking. OR for NAFLD: 1.38 (1.08, 1.77) and for Advanced Fibrosis: 2.20 (1.27, 3.82).
### Modest (~ < 2 Drinks/d) Alcohol Consumption Compared to Non-Drinking

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Design &amp; Population</th>
<th>Steatosis</th>
<th>NASH</th>
<th>Fibrosis</th>
<th>Severe liver event</th>
<th>HCC/ CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang Y., Hepatology 2019</td>
<td>Cohort study 4-Y FU N=190,048 Korean employees</td>
<td>Reduced risk</td>
<td>-</td>
<td>Increased risk</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chang Y., Hepatology 2018</td>
<td>Cohort study 8.3-Y FU N=58,927 Korean employees</td>
<td>-</td>
<td>-</td>
<td>Increased risk</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yamada K., PLOS ONE 2018</td>
<td>Cross-sectional study N=178 NAFLD</td>
<td>-</td>
<td>Reduced risk</td>
<td>Reduced risk</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Åberg F., Hepatology 2018</td>
<td>Follow-up data from national registers</td>
<td>-</td>
<td>-</td>
<td></td>
<td>Increased risk</td>
<td>-</td>
</tr>
<tr>
<td>Hagström H., Scand J Gastroenterol 2017</td>
<td>Cross-sectional N=120 NAFLD</td>
<td>-</td>
<td>No association</td>
<td>Reduced risk</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Moriya A., J of Hepatology 2015</td>
<td>Prospective 2-Y FU N=5297 Japanese</td>
<td>Reduced risk</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dunn W., J of Hepatology 2012</td>
<td>Cross-sectional N= 582 NASH CRN</td>
<td>-</td>
<td>Reduced risk</td>
<td>Reduced risk</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ascha MS., Hepetology 2010</td>
<td>Prospective 3-Y FU N=195 NASH-Cirrhosis</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>Increased risk</td>
</tr>
<tr>
<td>VanWagner LB., Gastroenterology 2017</td>
<td>Cross-sectional N=570 NAFLD</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>Not protective from subclinical CVD (e.g. CAC)</td>
</tr>
</tbody>
</table>
## Alcohol Recommendations for NAFLD from International Guidelines

<table>
<thead>
<tr>
<th>Association</th>
<th>Journal Year of publication</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Association for the Study of the Liver (EASL)</td>
<td>J of Hepatology 2016</td>
<td>Total abstinence is mandatory in NASH-cirrhosis</td>
</tr>
<tr>
<td>European Association for the Study of Diabetes (EASD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and European Association for the Study of Obesity (EASO)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Association for the Study of Liver Diseases (AASLD)</td>
<td>Hepatology 2017</td>
<td>There are insufficient data to make recommendations to non-heavy consumption of alcohol</td>
</tr>
<tr>
<td>The European Society for Clinical Nutrition and Metabolism (ESPEN)</td>
<td>Clinical Nutrition 2019</td>
<td>NAFL/NASH patients shall be encouraged to abstain from alcohol in order reduce risk for comorbidity and to improve liver biochemistry and histology</td>
</tr>
</tbody>
</table>
Practical Application of Lifestyle Management in Clinical Trials
Achieving Parity Across Sites
Improvement in Patients with NASH Under Lifestyle Intervention

- Even modest weight reduction (<5%) influences the entire spectrum of liver injury
- Improving dietary composition and/or physical activity?
- Fluctuations? Sampling error?

The Potential Confounding Effect of Lifestyle in NAFLD Medication RCTs
The change in confounder distributes differently between treatment arms.

The change in confounder significantly effects the outcome.

Potential confounder:
- BMI
- Waist circumference
- Dietary intake
- Physical activity
- Steatosis, NAS, Fibrosis

Randomization is not always enough:
- Theoretically, the groups have similar tendency for lifestyle change
- Practically, changes may be unbalanced
- Adjustment/stratification for change will reduce the statistical power
Does Weight Reduction Make the Added Value of Medication Negligible? (Even If Similar Between Arms)
Liver Fat Reduction Following ~5% Weight Reduction

Potential added value of medication – may be too small to be clinically and statistically significant

NAS/ Fibrosis Reduction Following ~5 – 7% Weight Reduction

Average reduction

Baseline >12 months

NAS (score) Treatment: 3 Baseline: 2
NAS (score) Placebo: 3 Baseline: 2
Fibrosis (stage) Treatment: 0.3 Baseline: 1.7
Fibrosis (stage) Placebo: 0.3 Baseline: 1.7

Vilar-Gomez E. Gastroenterology. 2015.
Next Step?

Diet X Medication Interaction

**Treatment arm**

The baseline or change in:

- Body fat
- Dietary intake
- Physical activity

Outcome

- Steatosis, Fibrosis, NAS progression

Treatment among obese/ more nutritionally altered

Treatment among less obese/ less nutritionally altered
Optional Lifestyle Related Exclusion Criteria at Screening

Recent weight reduction >5% of initial body weight
Recent significant change in dietary composition
Increase in exercise (≥ 150 min/w)

Advantages
• Mimics real life - Patients who can’t manage NAFLD by diet need medication
• Increased internal validity

Disadvantages
• Lower recruitment
• Lower external validity

Healthy liver ✔️
Fatty liver ❌
NASH/ Fibrosis ❌
What to Focus on in Dietary Intake Assessment?

• **Not calories**
  - Report bias
  - Better expressed in weight change

• **Yes dietary composition**
  - Fructose or sugar
  - Carbohydrates
  - Saturated fat
  - Soft drinks
  - Meat (red and processed)/ Fish
  - Olive oil

<table>
<thead>
<tr>
<th>Nutrient density - % of total calories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediterranean diet score (or other healthy eating index)</td>
</tr>
</tbody>
</table>
## Lifestyle Measures to Be Documented During the Trial for the Management of Confounding

<table>
<thead>
<tr>
<th>Lifestyle-related parameters</th>
<th>Ideal</th>
<th>Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline in:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight &amp; BMI</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Visceral adipose tissue (MRI)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Muscle mass (DEXA, BIA)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Dietary intake (questionnaires)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Mediterranean diet score/Healthy eating index</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical activity (questionnaires)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Supplements (e.g. omega-3, vitamin E)</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
What Lifestyle Advice to Provide? Uniform but NOT Comprehensive Dietary Intervention

General instructions

• Diet
• Physical activity
• No nutrition supplements

Justification

• Drugs aimed for patients who failed dieting
• Lack of comprehensive program mimics “real life”
• Uniform – within and across trials
• Ethics issues in long term trials
Obesity is feeding the rise in Non-Alcoholic Fatty Liver Disease (NAFLD) across Europe

In the absence of any licensed pharmacological therapies, policy measures and interventions must be implemented to prevent NAFLD.

NAFLD is caused by unhealthy lifestyles, excessive energy intake, poor diet, obesity, diabetes and pre-diabetes.